An enzymatic approach to fluorinated pharmaceuticals

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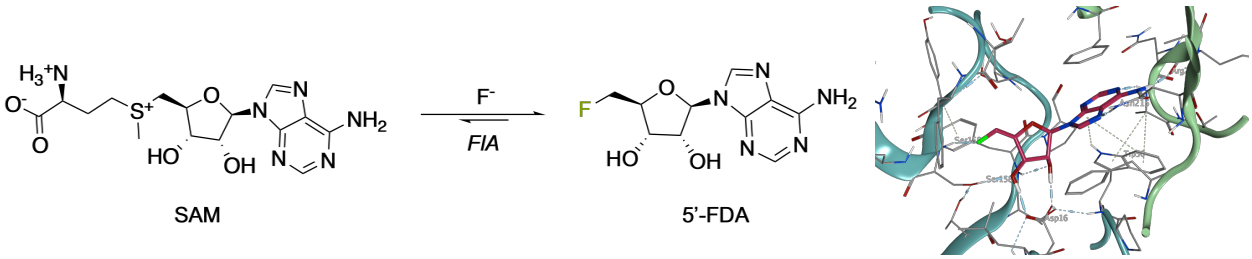
Fluorine plays a crucial role in pharmaceutical molecules and is currently present in 25% of all approved drugs due to its effects on pharmacokinetics and pharmacodynamics[1–3]. Furthermore, ^{18}F isotopes are commonly used for radiolabeling in PET scans because of their favorable half-life of 110 min[4]. Installation of fluorine via synthetic routes can be challenging because of its strong electronegative properties, lack of methods and catalysts, as well as slow reaction rates for radiolabeling[5–7]. In nature only one known enzyme mechanism has been found to catalyze C-F bond formation. The fluorinase enzyme (FlA, EC 2.5.1.63), first identified in *Streptomyces cattleya* in 2002,[8] facilitates the conversion of *S*-adenosyl-L-methionine (SAM) to 5'-fluoro-5'-deoxyadenosine (5'-FDA). Sixteen native FlA homologs have since been identified[9], several of which accept a limited number of non-native substrates[10–14]. The reaction proceeds via an S_N2-like mechanism under room temperature and aqueous conditions which contrasts the harsh conditions, specialized solvents and catalysts synthetic C-F bond formation often requires [10,15]. This work applied an interdisciplinary approach combining computational modeling and enzyme engineering for the development of enzymatic fluorination strategies for newly synthesized substrates and their use in PET labelling.



[1] S. Ali, X. Tian, S. A. Meccia, J. Zhou, *Eur. J. Med. Chem.* **2025**, *287*, 117380.
[2] H. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, et al., *ChemBioChem* **2004**, *5*, 637.
[3] M. C. Walker, M. C. Y. Chang, *Chem Soc Rev* **2014**, *43*, 6527.
[4] L. Wu, F. Maglangit, H. Deng, *Curr. Opin. Chem. Biol.* **2020**, *55*, 119.
[5] S. D. Schimler, S. J. Ryan, D. C. Bland, J. E. Anderson, M. S. Sanford, *J. Org. Chem.* **2015**, *80*, 12137.
[6] L. J. Allen, S. H. Lee, Y. Cheng, P. S. Hanley, J. M. Muhuhi, E. Kane, et al., *Org. Process Res. Dev.* **2014**, *18*, 1045.
[7] A. V. Mossine, A. F. Brooks, K. J. Makaravage, J. M. Miller, N. Ichiishi, M. S. Sanford, et al., *Org. Lett.* **2015**, *17*, 5780.
[8] D. O'Hagan, C. Schaffrath, S. L. Cobb, J. T. G. Hamilton, C. D. Murphy, *Nature* **2002**, *416*, 279.
[9] I. Pardo, D. Bednar, P. Calero, D. C. Volke, J. Damborský, P. I. Nikel, *ACS Catal.* **2022**, *12*, 6570.
[10] P. T. Lowe, I. Lüddecke, D. O'Hagan, *ChemBioChem* **2025**, *26*, e202400861.
[11] S. L. Cobb, H. Deng, A. R. McEwan, J. H. Naismith, D. O'Hagan, D. A. Robinson, *Org. Biomol. Chem.* **2006**, *4*, 1458.
[12] M. E. Sergeev, F. Morgia, M. R. Javed, M. Doi, P. Y. Keng, *J. Mol. Catal. B Enzym.* **2013**, *97*, 74.
[13] W. L. Yeo, X. Chew, D. J. Smith, K. P. Chan, H. Sun, H. Zhao, et al., *Chem. Commun.* **2017**, *53*, 2559.
[14] S. Thompson, I. N. Fleming, D. O'Hagan, *Org. Biomol. Chem.* **2016**, *14*, 3120.
[15] T. D. Ashton, P. J. Scammells, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3361.